UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/380,579	09/07/1999	SUSUMU IKEHARA	Q55691	2802

7590 03/04/2004

SUGHRUE MION ZINN MACPEAK & SEAS
2100 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 200373202

EXAMINER	
BELYAVSKYI, MICHAIL A	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/380,579	IKEHARA ET AL.	
	Examiner	Art Unit	
	Michail A Belyavskyi	1644	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 20 February 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires *4* months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☐ The proposed amendment(s) will not be entered because:
   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ they raise the issue of new matter (see Note below);
   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.
   NOTE: _____.
3. ☐ Applicant's reply has overcome the following rejection(s): _____.
4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.
6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7. ☐ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *9 and 10*.

   Claim(s) withdrawn from consideration: _____.
8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.
9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.
10. ☐ Other: _____

Continuation of 5. does NOT place the application in condition for allowance because: Applicant's arguments and the Examiner rebuttals are the same as in the previous Office Action mailed 10/20/2003.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:
(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 9-10 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Slavin , S et al., (US Patent 6,428,782) in view of Ildstad (US Patent. No. 5,514,364) and Zhang et al. (Eur. J. Immunol. 24 :1558-1565, IDS) for the same reasons set forth in the previous Office Action, mailed 10/20/2003

Applicant asserts that: (i)US Patent '782 does not teach total body irradiation (TBI) ; (ii) US Patent '364 does not disclose a technique usable for a one-day protocol by which an engraftment rate of 100% can be achived; (iii) Zhang et al merely teaches a technique without total body irradiation;

Applicants have traversed the primary and the secondary references pointing to the differences between the claims and the disclosure in each reference. Applicant is respectfully reminded that the rejection is under 35 USC103 and that unobviousness cannot be established by attacking the references individually when the rejection is based on the combination of the references. see In re Keller, 642 F.2d 4B, 208 USPQ 871, 882 (CCPA 1981) See MPEP 2145. This applicant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968).

As was stated in the previous Office Action, it is the Examiner position, that US Patent '782 teaches a method of inducing immunological tolerance in an organ transplantation recipient by subjecting the recipient to sublethal total body irradiation (TBI) and administering to the recipient whole bone marrow. Applicants attention is respectfully directed to column 8, lines 57-67, where it is specifically stated that " if TBI is used it should be at a dose level that causes no servere or irreversible pancytopenia. US Patent '782 teaches that transplanting of organ into recipient occurs within the same day as whole bone cells are administered (see column 13, lines 50-67, column 14, lines 10-15 and Example 14 in particular). US Patent '782 teaches engraftment rate of 100 % is achieved (see example 14 in particular).

US Patent '782 does not teaches that sublethal total body irradiation of at least 6.5 Gy or 6.5 Gy to 7.0 Gy and administering whole bone marrow cells by hepatic portal administration.

US Patent '364 teaches and claims a method of conditioning of a recipient intended for organ grafting by subjecting the recipient to sublethal total body irradiation and administering to the recipient whole bone marrow (see entire document, but especially the claims and columns 5, 8, 17 and 21-22). US Patent '364 also teaches that bone marrow engraftment after sublethal total body irradiation is reliably achieved in 100% of recipients at 7.0 Gy (see Figure 1 and column 17, especially lines 4-25). US Patent '364 further teaches transplantation of organs to the bone marrow recipient and exemplifies skin transplantation, showing that the recipients are specifically tolerant of the donor-type skin (see e.g., Abstract and columns 21-22).

Zhang et al. teach that in both intravenous and portal vein injections of bone marrow cells (BMC), most of the cells migrate to the liver, although more BMC do so after portal vein administration than after intravenous administration (see entire document, especially Figures 3 and 5 and page 1563 at the 4th full paragraph). Zhang et al. also review the art recognized prolongation of organ graft survival in a recipient when cells from the donor are administered to the recipient via the portal vein in addition to the transplanted organ, and note that this is due to a form of immunological tolerance (see especially the "Introduction" on page 1558 and the 1st paragraph of "Discussion" on page 1563).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of US Patent '364 and Zhang et al., to those of US Patent '782 to obtain a claimed method comprising administering to an organ transplant recipient total body sublethal irradiation of at least 6.5 Gy or 6.5 Gy to 7.0 Gy and administering whole bone marrow cells by hepatic portal administration.

One of ordinary skill in the art at the time the invention was made would have been motivated to combine sublethal irradiation about 7.0 Gy as taught by US Patent '364 , and administration of the bone marrow cells via the hepatic portal vein to provide an improved

method for inducing immunological tolerance in an organ transplantation recipient, as taught by Zhang et al with a method of inducing immunological tolerance in an organ transplantation recipient, taught by US Patent '782. Finally, given the art recognized time constraints associated with transplanting cells and organs from the same human donor; one of ordinary skill in the art would have also been motivated to transplant the organ within the same day as the whole bone marrow cells.

The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Semaker. 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. In re Aller, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

Specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Com. v. Electro Materials Corp. of America 202 USPQ 22 (DC SINY); and In re Burckel 201 USPQ 67 (CCPA).

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary..

Christina Chan

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600